Applicants respectfully traverse the rejection for the reasons set forth below.

Mendizabal Does Not Explicitly Anticipate
The Present Invention Under 35 U.S.C. §102(b)

It is settled law that a prior art reference must disclose all the elements of a claim in order to anticipate the invention recited by that claim. *See* M.P.E.P. §2131. There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Put another way, "[a] claim is anticipated and therefore invalid only when a single prior art reference discloses *each and every limitation of the claim*." *Glaxo Inc. v. Novapharm Ltd.*, 52 F.3d 1043, 1047, *cert. denied*, 116 S. Ct. 516 (1995) (citations omitted) (emphasis added).

Mendizabal discloses pharmaceutical compositions that contain *racemic* fluoxetine suitable for manufacturing *dispersable* tablets (*i.e.*, tablets that disintegrate in water in less than three minutes at 19°C - 21°C). *See, e.g.*, Mendizabal at page 5, lines 40-43. Such compositions are not encompassed by the pending claims. To be specific, Mendizabal does not disclose each and every element of claimed compositions. For example, Mendizabal does not disclose compositions that dissolve in greater than three minutes using the DISSOLUTION TEST, as recited by claims 13-20, 27, 29-32 and 37-38. Mendizabal further does not disclose compositions that are lactose-free, anhydrous, non-hygroscopic, or a combination thereof, as recited by claims 13-20, 22-29, 33-34 and 36. Because each of the pending claims recite a composition that is not disclosed by Mendizabal, Applicants respectfully submit that none of the pending claims are anticipated by that reference.

Mendizabal Does Not Inherently Anticipate
The Present Invention Under 35 U.S.C. §102(b)

On page 4 of the Final Office Action, it is alleged that even if each element of the claimed invention is not explicitly disclosed by Mendizabal, that element is inherently disclosed by the reference. In particular, it is alleged that various elements of the claimed inventions are inherently present in Mendizabal's disclosure. This assertion is respectfully traversed for the following reasons.

In the event that a reference does not explicitly teach all elements of a claim,

anticipation can only be shown by inherency if, and only if, the cited reference makes clear that the missing descriptive matter is *necessarily present* in the thing described in the reference and that it would be so recognized by one of ordinary skill in the art. *See In re Robertson*, 169 F.3d 743, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999) (citing *Continental Can Company USA Inc. v. Monsanto Company*, 948 F.2d 1264 (Fed. Cir. 1991)). Consequently, *inherency cannot be established by probabilities or possibilities*: "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to support an assertion of inherency." *In re Oelrich*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 414 (C.C.P.A. 1939)). Therefore, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." M.P.E.P. § 2112, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in the original).

In this case, the Examiner must therefore show that fluoxetine compositions that dissolve in *greater* than three minutes are *necessarily* disclosed by Mendizabal in order to rely upon the theory of inherency. However, Mendizabal is specifically directed to, and discloses, fluoxetine compositions that dissolve in *less* than three minutes. *See, e.g.*, Mendizabal at page 5, lines 40-41. Indeed, each example in Mendizabal (*i.e.*, Examples 1-20) discloses a dispersable tablet composition that disintegrates in water at 19°C to 21°C in less than three minutes. Mendizabal therefore cannot inherently disclose the compositions recited by claims 13-14, 16-18, 29-30 and 37-38. For this reason alone, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §102 be withdrawn.

On page 4 of the Final Office Action, it is further alleged that the compositions of this invention do not differ structurally or physically from those disclosed by Mendizabal. This assertion is respectfully traversed for the following reason.

In *Glaxo*, the Federal Circuit acknowledged that the prior disclosure of a polymorph (*i.e.*, a different crystalline form) of a compound does not anticipate the claimed compound. *Glaxo*, 52 F.3d at 1047. In that case, the claimed compound exhibited different *physical properties*, as evidenced by its x-ray powder diffraction and infrared absorption patterns, than those of the prior disclosed compound. *Id.* at 1047.

As in *Glaxo*, the compositions of this invention exhibit different physical properties than those disclosed by Mendizabal. Conveniently, these physical differences can

be measured using much less complicated analytical techniques than those relied on in *Glaxo*. In particular, the compositions recited by claims 13-14, 16-18, 29-30 and 37-38 dissolve at a substantially different rate (*i.e.*, greater than three minutes using the DISSOLUTION TEST) than those disclosed by Mendizabal. The significance of this physical property is apparent from Mendizabal itself.

Mendizabal discloses that the physical properties of disintegration rate and dispersion uniformity depend on the coadjuvants. The reference further makes it clear that since the disintegration rate is the critical parameter in the development of dispersable forms, the selection of the coadjuvants and the manufacturing process used is of the greatest importance. *See, e.g.*, Mendizabal at page 3, lines 18-23. Mendizabal thus discloses that "[t]he preparation of formulations for the manufacture of dispersable tablets requires . . . a search for suitable excipients enabling the requirements of the various *Pharmacopeas* to be fulfilled," one of which being that the dispersable tablets must dissolve in less than three minutes. *See, e.g.*, *Id.* at page 2, lines 53-55, page 3, lines 6-11 and page 5, lines 36-43.

Because the dissolution requirements of less than three minutes required by Mendizabal are met only by the painstaking and careful selection of the components of the compositions it discloses, it is clear that the physical properties of the compositions it discloses are different from those claimed by Applicants. For this reason as well as those discussed above, Applicants therefore respectfully submit that the rejection of claims 13-14, 16-18, 29-30 and 37-38 under 35 U.S.C. §102(b) is inappropriate, and should be withdrawn.[1]

For reasons much the same as those set forth above, Applicants respectfully submit that none of the other compositions recited by the pending claims are inherently disclosed by Mendizabal. To be specific, claims 22-25, 28-29 and 36 recite anhydrous or non-hygroscopic formulations, *e.g.*, formulations that are substantially free of unbound water. *See, e.g.*, Specification at page 10, lines 16-25 and page 11, lines 6-25. Consequently, an assertion that these claims are inherently disclosed by Mendizabal must be supported by "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." M.P.E.P. § 2112. The anhydrous or non-hygroscopic characteristics of the compositions

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[1] If, however, the Examiner is aware of facts not disclosed by the cited art that do affect the novelty of claims 13-14, 16-18, 29-30 and 37-38, Applicants respectfully request that she set forth such facts in an affidavit pursuant to 37 C.F.R. §104(d)(2).

recited by claims 22-25, 28-29 and 36 are *not*, however, necessarily found in those disclosed by Mendizabal.

To be specific, Mendizabal fails to take precautions to avoid water or moisture in formulations of fluoxetine and is silent – at best – regarding the use of formulations that are anhydrous or non-hygroscopic. For example, Mendizabal uses conventional direct compression to avoid the inclusion of *additional* external water from the atmosphere, it admits the incorporation of water. *See, e.g.*, Mendizabal at page 5, lines 26-31. Mendizabal further does not disclose a drying process, which would ensure that each component itself is substantially free of unbound water.[2] *See, e.g., id.* at page 5, lines 26-31. In addition, Mendizabal avoids coadjuvants, such as standard stearic acid salts, that do *not* adsorb water and further selects antiadherents that capture humidity. *See, e.g., id.* at page 4, lines 36-37 and 40-44. Because of their very nature, these Mendizabal compositions contain water that is adsorbed by such components. Applicants respectfully submit, therefore, that it cannot be asserted that *each and every* composition disclosed by Mendizabal is anhydrous or non-hygroscopic. Consequently, Applicants respectfully request that the rejection of claims 22-25, 28-29 and 36 under § 102 be withdrawn.[3]

In sum, Applicants respectfully submit that claims 13-14, 16-18, 22-25, 28-30, and 35-38 are novel and not anticipated by Mendizabal, and request that the rejection under 35 U.S.C. § 102(b) be withdrawn.[4]

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[2] On pages 4-5 of the Final Office Action, it is alleged that the lack of a drying process in Mendizabal is not germane to the patentability of the claimed compositions. Applicants, however, respectfully submit that a drying process is *essential* in producing anhydrous or non-hygroscopic compositions. Mendizabal discloses compositions that adsorb water or capture humidity. *See, e.g.*, Mendizabal at page 4, lines 36-37 and 40-44. Thus, in the absence of a drying process, the compositions of Mendizabal would contain unbound water.

[3] In addition, Applicants point out that claims 21 and 36 recite the language "consisting essentially of," which excludes all ingredients that materially affect a basic and novel characteristic of the compositions they claim (*i.e.*, a stable formulation). Thus, claims 21 and 36 exclude amounts of lactose or water from the composition of the tablet that would render it unstable. Such compositions are also not disclosed by Mendizabal.

[4] Claim 29 is dependent on claims 1, 13, 14, 21, 23, and 24, each of which are not anticipated by Mendizabal for the reasons above. In addition, claim 35 is dependent on claims 13-14, 21, 23-24, and 30, each of which are not anticipated by Mendizabal for the reasons above. Thus, claims 29 and 35 cannot be anticipated by Mendizabal.

The Rejection Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-38 were rejected under 35 U.S.C. § 103(a) as being obvious over Mendizabal in view of the Physicians Desk Reference ("PDR"), 50th ed. (1996) for the reasons set forth on pages 5-7 of the Final Office Action. Applicants respectfully traverse the rejection for the reasons set forth below.

The present invention recites lactose-free formulations (*see, e.g.*, claims 1-22, 24, 29, 33-34, and 36-37), anhydrous or non-hygroscopic formulations (*see, e.g.*, claims 22-29 and 36), formulations containing an optically pure enantiomer of fluoxetine (*see, e.g.*, claims 1-34 and 36-38), formulations that dissolve and disperse in greater than three minutes (*See, e.g.*, claims 13-20, 27, 29-32 and 37-38), and methods using such formulations for the treatment of depression (*See, e.g.*, claim 35).

Mendizabal does not disclose or suggest chemically stable, anhydrous, or non-hygroscopic formulations containing racemic fluoxetine or a pharmaceutically acceptable salt thereof. In addition, Mendizabal does not disclose or suggest formulations containing an optically pure enantiomer of fluoxetine, the unexpected benefits of lactose-free formulations, or formulations that disintegrate in greater than three minutes.

The PDR fails to remedy the deficiencies of Mendizabal. The PDR discloses a formulation comprising only *racemic* fluoxetine, even though it states that, "[i]n animal models, both enantiomers are specific and potent serotonin uptake inhibitors *with essentially equivalent pharmacologic activity*." PDR at 919 (emphasis added). The PDR therefore does not suggest pharmaceutical compositions that comprise an optically pure enantiomer of fluoxetine. Instead, the PDR discloses that racemic, optically pure S-fluoxetine, and optically pure R-fluoxetine are specific and potent serotonin uptake inhibitors, and that of the three, only racemic fluoxetine had been shown to be safe and effective. *Id.* At the time of this invention, the PDR would therefore have taught away from the optically pure fluoxetine compositions of this invention. Indeed, this conclusion would have been a natural one to those skilled in the art, who would have understood that the separation of enantiomers can be costly. For these reasons, Applicants respectfully submit that the compositions recited by claims 1-34 and 36-38 are not obvious in view of Medizabal and the PDR, and request that their rejection under § 103 be withdrawn.[5]

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[5] Claim 35, which is directed to a method of treating depression, is dependent (continued...)

The PDR also does not disclose or suggest anhydrous or non-hygroscopic formulations containing racemic fluoxetine, an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, as recited by claims 22-29 and 36. Consequently, the PDR adds nothing to Mendizabal that would suggest the anhydrous or non-hygroscopic formulations recited in claims 22-29 and 36, and Applicants respectfully request that the rejection of these claims under § 103 be withdrawn.

On pages 6-7 of the Final Office Action, it is alleged that it would be obvious and well within the capability of the skilled artisan not to use a disintegrant as recited by, for example, claims 15 and 21. However, Mendizabal discloses dispersable tablets that completely disintegrate within three minutes in water at 19°C-21°C, and makes clear that the disintegration rate is *dependent* on the use of disintegrants. *See, e.g.*, Mendizabal at page 5, lines 40-43 and page 2, lines 12-16. Mendizabal therefore teaches away from fluoxetine compositions that do not contain a disintegrant.

Furthermore, Mendizabal and the PDR relate to distinct formulations made for different purposes. In particular, Mendizabal is directed to rapidly disintegrating compressed *tablets*, while the PDR is directed to Pulvule® *capsule* formulations. In other words, one of ordinary skill in the art aware of these two cited references at the time of the invention would not have been motivated to combine the rapidly dispersing formulations of Mendizabal with the capsule formulation in the PDR. Even if there were a suggestion to combine the references, when combined, the references do *not* disclose or suggest the dissolution of the compounds in greater than three minutes and the improved stability of the claimed compositions, much less even recognize the problem with lactose-containing tablets. The combination of these references would lead one of ordinary skill in the art to formulations that disintegrate in *less* than three minutes. The present invention, however, recites tablets and compositions that are understood to *not* rapidly disintegrate in less than three minutes, *i.e.*, the tablets and compositions disintegrate in *greater* than three minutes. Thus, there would be no motivation to prepare a lactose-free compressed tablet when capsule technology is combined with disintegrating tablet technology.

For the foregoing reasons, Mendizabal and the PDR, whether taken alone or in

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[5] (...continued)
on claims 13-14, 21, 23-24, and 30. Because none of these are anticipated or obvious over Mendizabal, Applicants respectfully submit that the rejection of claim 35 should be withdrawn.

combination, do not disclose or suggest the claimed invention. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Mendizabal and the PDR be withdrawn.

Finally, claims 1-38 were rejected under 35 U.S.C. § 103(a) as being obvious over Mendizabal in view of the PDR, and further in view of Wirth *et al.*, *J. Pharm. Sci.*, 87(1):31-39, 1998 ("Wirth"). Applicants respectfully traverse the rejection for the reasons set forth below.

Although Wirth discloses that tablets containing fluoxetine are unstable since fluoxetine undergoes the Maillard reaction with lactose, Wirth does not remedy the deficiencies of Mendizabal or the PDR. In particular, Wirth does not disclose, much less suggest, pharmaceutical compositions that: a) dissolve in greater than three minutes when subjected to a DISSOLUTION TEST; b) are anhydrous or non-hygroscopic or c) contain an optically pure enantiomer of fluoxetine.

Furthermore, Mendizabal and Wirth relate to formulations made for different purposes. Mendizabal is only concerned with tablet formulations that *rapidly* disperse, whereas Wirth is directed to *conventional* lactose-containing tablets as compared to the specific Pulvule® capsule formulation. *See* Wirth at 32. In other words, one of ordinary skill in the art aware of these two cited references at the time of the invention would *not* have been motivated to combine the rapidly dispersing formulations of Mendizabal with the formulations tested in Wirth. Even if there were a suggestion to combine the references, when combined they do not suggest, for example, lactose-free tablets that disintegrate in greater than three minutes, such as are recited by, for example, claims 13-20, 22 and 29.

In sum, Mendizabal, the PDR, and Wirth, whether taken individually or in any combination, do not disclose or suggest chemically stable, lactose-free, anhydrous, or non-hygroscopic formulations containing racemic fluoxetine, an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof which further dissolve or disperse uniformly in greater than three minutes as presently claimed. Further, since there is no motivation to combine Mendizabal and the PDR or Mendizabal and Wirth, there is no motivation to combine Mendizabal with the PDR and with Wirth. For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-38 under 35 U.S.C. §103(a) over Mendizabal, the PDR and Wirth.

CONCLUSION

Applicants believe that all pending claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner deem it helpful, a personal or telephone interview is respectfully requested to discuss any remaining issues in an effort to expeditiously advance the application to allowance.

No fee is believed to be due for this submission. Please charge the required fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: March 23, 2000

P45,479

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